REMARKS

Applicants request reconsideration of the pending claims in view of the amendments above and the remarks below.

I. Pending Claims

Claims 22-35 were pending. Applicants note that the elected invention encompasses independent claim 22. The Examiner withdrew claims 34 and 35 as being not corresponding to the elected invention. But these claims, as indicated by the Examiner in the March 23, 2007 Restriction Requirement, are part of the elected invention. Applicants note that the species election is provisional, and the species is only elected in the event that the generic claims are not found patentable. Applicants believe that it is thus improper not to consider these claims at this time.

Applicants have canceled claim 29 without prejudice.

Applicants have amended claims 22-25, 28, 30 and 33 to conform with applicants' election of invention in response to the March 23, 2007 Restriction Requirement. No new matter is introduced.

Applicants have amended claims 22 (and claims dependent therefrom) and 33-35, replacing "non-human transgenic animal" with "transgenic rodent." This amendment is supported in the Specification throughout. See, for example, the Specification at page 25, lines 30-32. Hence, no new matter is introduced.

Applicants have amended claim 30 to improve its form by reciting: "a stress inducible promoter *which is* operatively isolated from a nucleic acid sequence encoding beta-lactoglobulin by a nucleotide sequence flanked by nucleic acid sequences recognized by a site specific recombinase, or by insertion such that it is inverted with respect to the transcription unit encoding beta-lactoglobulin (amendment discussed is italicized)" No new matter is introduced.

Applicants have amended claim 33 to recite: "comprising the step of detecting a gene activation event in a cell *in vivo*, comprising assaying said transgenic rodent whose cells express a nucleic acid construct as defined in claim 24, in which the rodent is subjected to a gene activation event that is signaled by expression of a peptide tagged beta-lactoglobulin reporter gene, wherein the gene activation event is the result of toxicological stress." This amendment is supported in the Specification throughout. See, for example, claims 22 and 24 and the Specification at page 27, lines 6-8. Hence, no new matter is introduced.

Applicants have also amended claim 25 by deleting reference to 'accession no. X12817" and replacing it with "SEQ ID NO: 23." This amendment is supported in the Specification throughout. See, for example, the Specification at page 36, lines 30-31.

After the amendment, claims 22-28 and 30-35 are pending.

Applicants reserve the right to prosecute canceled subject matter in this application, a continuing application or a related application.

I. Election/Restriction

The Examiner has made final the September 21, 2007 species election requirement. Applicants acknowledge that the Examiner has considered applicants' traversal arguments and was not persuaded by those arguments. Therefore, applicants explicitly (removing the provisional nature of applicants' election) elect species A, induction of toxicological stress. Applicants note that at least pending claims 22-28 and 30-33 are generic claims. Accordingly, applicants have satisfied this election of species.

II. Objection to the Specification

The specification was objected to because the term "CLAIMS" on page 50 is improper. Applicants have replaced the term "CLAIMS" with the term "WE CLAIMS:," and thus overcoming this objection.

The Examiner objected to the Specification for not complying with the sequence identifier requirement. Applicants submitted a Sequence Listing on October 24, 2005. That Sequence Listing was accompanied by amendments to the Specification, which amendments incorporated sequence identifiers throughout the specification. The sequences in Figures 7-9, 15, 18-23 are properly identified by sequence identifiers in these amendments. The Examiner also stated that there is no sequence identifier for the nucleotide sequences on pages 11, 12, 38, 44 and 45. But applicants provided such sequence identifier on those pages of the specification in the October 24, 2005 Amendment. Hence, applicants request withdrawal of this objection.

The Examiner objected to the specification for containing hyperlinks and/or other forms of browser-executable codes. Applicants did not delete these hyperlinks and/or other forms of browser-executable codes because applicants are not attempting to incorporate the contents of the sites to which the links are directed to. Rather, these hyperlinks and/or other forms of browser-executable codes are part of the written description. See MPEP 608.01. Accordingly, applicants request withdrawal of this objection.

III. Claim Rejection: 35 U.S.C. §112, Second Paragraph

Claim 25 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite with respect to the recitation of "accession no. X12817." Applicants have amended claim 25 by deleting reference to 'accession no. X12817" and replacing it with "SEQ ID NO: 23." This rejection is thus overcome.

Claims 30 and 31 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Applicants traverse.

The Examiner stated that claim 30 (and its dependent claim 31) is vague because of its recitation "a stress inducible promoter operatively isolated from a nucleic acid sequence encoding beta-lactoglobulin by a nucleotide sequence flanked by nucleic acid sequences recognized by a site specific recombinase, or by insertion such that it is inverted with respect to the transcription unit encoding beta-lactoglobulin." Applicants have amended claim 30 to improve its form by reciting: "a stress inducible promoter *which is* operatively isolated from a nucleic acid sequence encoding beta-lactoglobulin by a nucleotide sequence flanked by nucleic

acid sequences recognized by a site specific recombinase, or of insertion such that it is inverted with respect to the transcription unit encoding beta-lactoglobulin."

Applicants submit that the term "operatively isolated" is clear to a person skilled in the art. The term "operatively linked" is commonly used when referring to promoter sequences that are sufficiently linked to a gene to control the expression of that gene. The term "operatively isolated" means the opposite of "operatively linked," i.e., that the promoter does not control the expression of that gene.

Applicants believe that these amendments to claim 30 and the understanding of the term "operatively isolated" explain exactly how the stress inducible promoter is operatively isolated from the nucleic acid encoding a member of the lipocalin family (in this case, beta-lactoglobulin). Accordingly, applicants believe that amended claim 30 (and its dependent claim 31) are not indefinite.

Claim 33 stand rejected under 35 U.S.C. §112, second paragraph, for allegedly omitting essential steps. Applicants have amended claim 33 to recite: "comprising the step of detecting a gene activation in a cell *in vivo*, comprising assaying said transgenic rodent whose cells express a nucleic acid construct as defined in claim 24, in which the rodent is subjected to a gene activation event that is signaled by expression of a peptide tagged beta-lactoglobulin reporter gene, wherein the gene activation event is the result of toxicological stress." Amended claim 33 contains the omitted essential step, thus obviating this rejection.

IV. Claim Rejection: 35 U.S.C. §112, first Paragraph, Written Description

Claims 22-28 and 30-33 stand rejected under 35 U.S.C. §112, First Paragraph, for allegedly not complying with the written description requirement. Applicants traverse.

The Examiner contends that the claims encompass "the use of tens of thousands of different transgenic non-human animals." Applicants have amended the pending claims to recite "transgenic rodent" instead of "transgenic non-human animal." The amended pending claims thus encompass much fewer animals than the un-amended claims that were pending before. Transgenic rodent models are clearly well developed in the art.

The Examiner also contends that the Specification contains limited disclosure regarding the transgenic non-human animals such that the disclosure would not convey to one skilled in the art that the inventors were in possession of the claimed transgenic non-human animals. Applicants disagree.

Applicants submit herewith a Declaration of Dr. Bruce Whitelaw[1] (the "Whitelaw Declaration"), one of the inventors of this application.

Dr. Whitelaw states that "a person skilled in this field . . . would believe that the inventors had possession of the invention now claimed." The Whitelaw Declaration, ¶10. Dr. Whitelaw makes this statement on the basis, among others, that "the Examples of the present application provide sufficient information to a person of skill in the art to produce a transgenic rodent as now claimed in the present invention." The Whitelaw Declaration, ¶5.

[1] Applicants note that the Whitelaw Declaration contains a typographical error and refers to this application as 10/522,536 rather than 10/522,356.

Specifically, Dr. Whitelaw points to Example 11 as providing "guidance regarding the expression of epitope tagged lipocalin reporter proteins in transgenic animals." The Whitelaw Declaration, ¶6. Dr. Whitelaw further states that "Example 11 teaches that transgenic animals can be generated using one of several standard methods in the art including pronuclear injection, blastocyst injection of transfected cells or using viral vectors. These methods were well known in the art at the priority date of the present invention and a skilled person would readily be able to carry out these methods using their knowledge and the teachings of the scientific papers referred to on page 48, lines 15 to 19 of the present application." The Whitelaw Declaration, ¶6. Clearly, the Specification teaches how to make the claimed transgenic rodents.

Dr. Whitelaw further states that "Example 11 also gives specific guidance as to how to product (sic) transgenes containing the Cyp1a1 promoter sequence driving expression of myc epitope tagged BLG reporter, as described on page 48, line 25 to page 49, line 7." The Whitelaw Declaration, ¶7. He also states that "[t]he Cyp1a1 promoter is [] well described and characterised in the art, for example in WO 97/23635." The Whitelaw Declaration, ¶9. Clearly, the Specification contains enough teaching on making a transgene.

Finally, Dr. Whitelaw states that the application provides guidance on identifying positive transgenic animals by analysis of the DNA. The Whitelaw Declaration, ¶8. He further states that "[p]age 49, lines 9 to 15 of the present application also demonstrates how to detect and screen for a gene activation event of toxicologically induced stress. In particular, page 49, lines 10 to 15 specify that transgenic animals are exposed to stress, for example by drug

administration, and blood and urine samples are collected over time. Samples collected pre- and post-insult are analysed for the presence of the tagged lipocalin by methods including Western blot and ELISA. Depending on the specific insult or inducing agent an increase or decrease in reporter activity are detected." The Whitelaw Declaration, ¶8. Accordingly, the Specification teaches several methods to detect, identify and monitor the claimed transgenic rodents.

Accordingly, the Specification contains specific teaching on how to make the claimed transgenic rodents to convey to a person skilled in the art that the inventors had possession of the claimed rodents. Applicants have thus overcome this rejection of lack written description.

V. Claim Rejection: 35 U.S.C. §112, first Paragraph, Enablement

For reasons stated in the December 14, 2007 Office Action, claims 22-28 and 30-33 stand rejected under 35 U.S.C. §112, First Paragraph, for allegedly not being enabled. Applicants traverse.

The Examiner contends that the claims encompass "the use of tens of thousands of different transgenic non-human animals." Applicants have amended the pending claims to recite "transgenic rodent" instead of "transgenic non-human animal." The amended pending claims thus encompass much fewer animals than the un-amended claims that were pending before. Transgenic rodent models are clearly well developed in the art.

The Examiner contends that applicants do not have possession of the claimed transgenic animal, the lack of non-mouse ES cells for making transgenic animals and that the phenotype of transgenic animal was unpredictable. Applicants disagree.

Applicants submit herewith a Declaration of Dr. Bruce Whitelaw (the "Whitelaw Declaration"), one of the inventors of this application.

Dr. Whitelaw states that "a person skilled in this field would be able to put the invention into practice using the disclosure of the present invention and would believe that the inventors had possession of the invention now claimed." The Whitelaw Declaration, ¶10. Dr. Whitelaw makes this statement on the basis, among others, that "the Examples of the present application provide sufficient information to a person of skill in the art to produce a transgenic rodent as now claimed in the present invention." The Whitelaw Declaration, ¶5.

Specifically, Dr. Whitelaw points to Example 11 as providing "guidance regarding the expression of epitope tagged lipocalin reporter proteins in transgenic animals." The Whitelaw Declaration, ¶6. Dr. Whitelaw further states that "Example 11 teaches that transgenic animals can be generated using one of several standard methods in the art including pronuclear injection, blastocyst injection of transfected cells or using viral vectors. These methods were well known in the art at the priority date of the present invention and a skilled person would readily be able to carry out these methods using their knowledge and the teachings of the scientific papers referred to on page 48, lines 15 to 19 of the present application." The Whitelaw Declaration, ¶6. Clearly, the Specification teaches how to make the claimed transgenic rodents.

Dr. Whitelaw further states that "Example 11 also gives specific guidance as to how to product (sic) transgenes containing the Cyp1a1 promoter sequence driving expression of myc epitope tagged BLG reporter, as described on page 48, line 25 to page 49, line 7." The

Whitelaw Declaration, ¶7. He also states that "[t]he Cyp1a1 promoter is [] well described and characterised in the art, for example in WO 97/23635." The Whitelaw Declaration, ¶9. Clearly, the Specification contains enough teaching on making a transgene.

Finally, Dr. Whitelaw states that the application provides guidance on identifying positive transgenic animals by analysis of the DNA. The Whitelaw Declaration, ¶8. He further states that "[p]age 49, lines 9 to 15 of the present application also demonstrates how to detect and screen for a gene activation event of toxicologically induced stress. In particular, page 49, lines 10 to 15 specify that transgenic animals are exposed to stress, for example by drug administration, and blood and urine samples are collected over time. Samples collected pre- and post-insult are analysed for the presence of the tagged lipocalin by methods including Western blot and ELISA. Depending on the specific insult or inducing agent an increase or decrease in reporter activity are detected." The Whitelaw Declaration, ¶8. Accordingly, the Specification teaches several methods to detect, identify and monitor the claimed transgenic rodents. The Specification also provides explicit teaching on using the claimed transgenic rodents for detecting a gene activation event of toxicologically induced stress.

Accordingly, the Specification contains specific teaching on how to make and use the claimed transgenic rodents.

The Examiner also contends that it is unpredictable which amino acids can be removed from a protein's sequence and still result in similar activity. Applicants believe that the art at the

time was sufficiently advanced to allow for making amino acid deletions, assaying for protein activity, and picking the proteins with activity, without undue experimentation.

Applicants have thus overcome the lack-of-enablement rejection.

VI. Conclusion

It is respectfully requested that the Examiner enter the present amendments, reconsider the rejections based on the amendments and remarks above and pass the present application to issue.

Please charge all fees due in connection with this paper and accompanying papers to Wilmer Cutler Pickering Hale and Dorr LLP Deposit Account No. 08-0219.

Respectfully submitted,

By /Stanley D. Liang/
Stanley D. Liang, Ph.D.
Attorney for Applicant(s)
Registration No. 43,753

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WILMER CUTLER PICKERING HALE AND DORR, LLP
399 Park Avenue
New York, NY 10022
Telephone: (212) 295-6318
Facsimile: (212) 230-8888